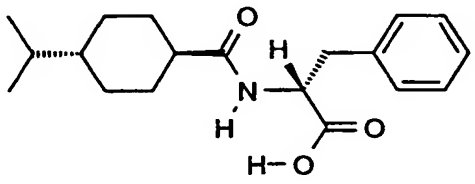
Method of treating metabolic disorders

The invention relates to a combination, such as a combined preparation or pharmaceutical composition, respectively, which comprises nateglinide and (a) an antidiabetic phenylacetic acid derivative or (b) acarbose for simultaneous, separate or sequential use in the prevention, delay of progression or treatment of diseases, especially metabolic disorders and in particular type 2 diabetes and di seases and conditions associated with diabetes; the use of such combination for the preparation of a medicament for the prevention, delay of progression or treatment of metabolic disorders; the use of such combination for the cosmetic treatment of a mammal in order to effect a cosmetically beneficial loss of body weight; a method of prevention, delay of progression or treatment of diseases, especially diabetes, in warm-blooded animals; a method of improving the bodily appearance of a warm-blooded animal.

The generally accepted aims in the treatment of diabetes are to provide relief from symptoms, improvement of the quality of life and prevention of both acute (hyperosmolar coma and ketoacidosis) and chronic complications (e.g. diabetic neuropathy, diabetic nephropathy and premature atherosclerosis). Type 2 diabetes is characterized by both increased peripheral insulin resistance and abnormal insulin secretion. At least two abnormalities of insulin secretion are recognized: in the first phase insulin is both delayed and inadequate in the face of elevated circulating glucose levels and in the second phase insulin secretion is lost. Several metabolic, hormonal, and pharmacological entities are known to stimulate insulin secretion including glucose, amino-acids and gastrointestinal peptides. The Diabetes Control and Complications Trial (DCCT) performed in Type I IDDM subjects has established that lowering of blood glucose is associated with decreases in the onset and progression of diabetic microvascular complications (Diabetes Control and Complications Trial Research Group; N. Engl. J. Med. 1993, 329, 977-986). Therefore, one therapeutic focus is on optimizing and potentially normalizing glycemic control in subjects with type 2 diabetes. Presently available oral agents needed to be improved in order to better meet this therapeutic challenge.

The present invention relates to a combination, such as a combined preparation or

pharmaceutical composition, respectively, which comprises nateglinide of formula (I)



(I)

and (a) an antidiabetic phenylacetic acid derivative or (b) acarbose, in which the active ingredients are present in each case in free form or in the form of a pharmaceutically acceptable salt and optionally at least one pharmaceutically acceptable carrier; for simultaneous, separate or sequential use, particularly in the prevention, delay of progression or treatment of diseases, especially metabolic disorders and in particular type 2 diabetes mellitus and diseases and conditions associated with diabetes mellitus. Such a combination is preferably a combined preparation or a pharmaceutical composition.

By the term "a combined preparation or pharmaceutical composition, respectively, which comprises nateglinide and (a) an antidiabetic phenylacetic acid derivative or (b) acarbose, in which the active ingredients are present in each case in free form or in the form of a pharmaceutically acceptable salt and optionally at least one pharmaceutically acceptable carrier, for simultaneous, separate or sequential use", there is meant especially a "kit of parts" in the sense that the components nateglinide and (a) an antidiabetic phenylacetic acid derivative or (b) acarbose can be dosed independently or by use of different fixed combinations with distinguished amounts of the components, i.e. at different time points or simultaneously. The parts of the kit of parts can then e.g. be administered simultaneously or chronologically staggered, that is at different time points and with equal or different time intervals for any part of the kit of parts. Preferably, the time intervals are chosen such that the effect on the treated disease or condition in the co mbined use of the parts is larger than the effect which would be obtained by use of only any one of the components. Preferably, there is at least one beneficial effect, e.g. a mutual enhancing of the effect of nateglinide and (a) an antidiabetic phenylacetic acid derivative or (b) acarbose, additional advantageous effects, less side effects, a combined therapeutical effect in a non-effective dosage of on or each of the components and (a) an antidiabetic phenylacetic acid derivative or (b) acarbose, and especially a synergism, e.g. a more than additive effect,

between nateglinide and (a) an antidiabetic phenylacetic acid derivative or (b) acarbose

The term "prevention" means prophylactic administration of the combination, such as a combined preparation or pharmaceutical composition, to healthy patients to prevent the outbreak of the diseases and conditions mentioned herein. Moreover, the term "prevention" means prophylactic administration of such combination to patients being in a pre-stage of the disease, especially diabetes, to be treated. The term "delay of progression" used herein means administration of the combination, such as a combined preparation or pharmaceutical composition, to patients being in a pre-stage of the disease, especially diabetes, to be treated in which patients a pre-form of the corresponding disease is diagnosed.

"Diseases and conditions associated with diabetes mellitus" as defined in this application comprise, but are not limited to hyperglycemia, hyperinsulinaemia, hyperlipidaemia, insulin resistance, impaired glucose metabolism, obesity, diabetic retinopathy, macular degeneration, cataracts, diabetic nephropathy, glomerulosclerosis, diabetic neuropathy, erectile dysfunction, premenstrual syndrome, vascular restenosis and ulcerative colitis. Furthermore, "diseases and conditions associated with diabetes mellitus" comprise, but are not limited to: coronary heart disease, hypertension, angina pectoris, myocardial infarction, stroke, skin and connective tissue disorders, foot ulcerations, metabolic acidosis, arthritis, osteoporosis and in particular conditions of impaired glucose tolerance.

Furthermore, the invention relates to a combined preparation or pharmaceutical composition, respectively, which comprises nateglinide and (a) an antidiabetic phenylacetic acid derivative or (b) acarbose, wherein the combined preparation or pharmaceutical composition, respectively, comprises at least one further pharmaceutically active compound e.g. selected from the group consisting of antidiabetic thiazolidinediones, sulphonyl urea derivatives, metformin, and insulin, or the pharmaceutically acceptable salts of such compounds where possible; or at least one further antidiabetic phenylacetic acid derivative or a pharmaceutically acceptable salt thereof.

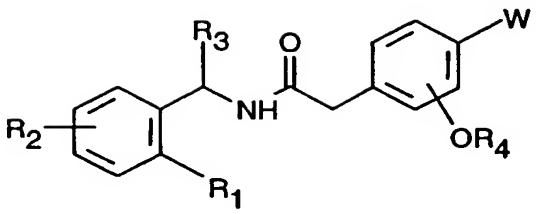
Acarbose is O-4,6-dideoxy-4-{[1S,4R,5S,6S]-4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexen-1-yl]-amino}-α-D-glucopyranosyl-(1→4)-O-α-D-glucopyranosyl-(1→4)-D-glucopyranose.

Repaglinide is (S)-2-ethoxy-4-{2-[[3-methyl-1-[2-(1-piperidinyl)phenyl]butyl]amino]-2-oxoethyl}benzoic acid.

An antidiabetic thiazolidinedione is, for example, (S)-((3,4-dihydro-2-(phenyl-methyl)-2H-1-benzopyran-6-yl)methyl-thiazolidine-2,4-dione (englitazone), 5-{[4-(3-(5-methyl-2-phenyl-4-oxazolyl)-1-oxopropyl)-phenyl]-methyl}-thiazolidine-2,4-dione (darglitazone), 5-{[4-(1-methyl-cyclohexyl)methoxy)-phenyl]methyl}-thiazolidine-2,4-dione (ciglitazone), 5-{[4-(2-(1-indolyl)ethoxy)phenyl]methyl}-thiazolidine-2,4-dione (DRF2189), 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)-ethoxy)]benzyl}-thiazolidine-2,4-dione (BM-13.1246), 5-(2-naphthylsulfonyl)-thiazolidine-2,4-dione (AY-31637), bis{4-[(2,4-dioxo-5-thiazolidinyl)methyl]phenyl}methane (YM268), 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)-2-hydroxyethoxy]benzyl}-thiazolidine-2,4-dione (AD-5075), 5-[4-(1-phenyl-1-cyclopropanecarbonylamino)-benzyl]-thiazolidine-2,4-dione (DN-108) 5-{[4-(2-(2,3-dihydroindol-1-yl)ethoxy)phenyl]methyl}-thiazolidine-2,4-dione, 5-[3-(4-chloro-phenyl])-2-propynyl]-5-phenylsulfonyl)thiazolidine-2,4-dione, 5-[3-(4-chlorophenyl])-2-propynyl]-5-(4-fluorophenyl-sulfonyl)thiazolidine-2,4-dione, 5-{[4-(2-(methyl-2-pyridinyl-amino)-ethoxy)phenyl]methyl}-thiazolidine-2,4-dione (rosiglitazone), 5-{[4-(2-(5-ethyl-2-pyridyl)ethoxy)phenyl]-methyl}thiazolidine-2,4-dione (pioglitazone), 5-{[4-((3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy)-phenyl]-methyl}-thiazolidine-2,4-dione (troglitazone), 5-[6-(2-fluoro-benzyloxy)naphthalen-2-ylmethyl]-thiazolidine-2,4-dione (MCC555), 5-{[2-(2-naphthyl)-benzoxazol-5-yl]-methyl}thiazolidine-2,4-dione (T-174) and 5-(2,4-dioxothiazolidin-5-ylmethyl)-2-methoxy-N-(4-trifluoromethyl-benzyl)benzamide (KRP297).

A sulphonyl urea derivative is, for example, glisoxepid, glyburide, acetohexamide, chloro-propamide, glibornuride, tolbutamide, tolazamide, glipizide, carbutamide, gliquidone, glyhexamide, phenbutamide or tolcyclamide; and preferably glimepiride or gliclazide.

Nateglinide (EP 196222 and EP 526171), repaglinide (II, in which R_1 is 1-piperidinyl, R_2 is hydrogen, R_3 is 2-methylpropyl, R_4 is ethyl and W is carboxy; EP 0 147 850 A2, in particular Example 11 on page 61, and EP 0 207 331 A1),



(II)

acarbose (US 4,062,950), pioglitazone (EP 0 193 256 A1), rosiglitazone (EP 0 306 228 A1), troglitazone (EP 0 139 421), englitazone (EP 0 207 605 B1), KRP297 (JP 10087641-A), MCC555 (EP 0 604 983 B1), darglitazone (EP 0 332 332), AY-31637 (US 4,997,948), ciglitazone (US 4,287,200) are in each case generically and specifically disclosed in the documents cited in brackets beyond each substance, in each case in particular in the compound claims and the final products of the working examples, the subject-matter of the final products, the pharmaceutical preparations and the claims are hereby incorporated into the present application by reference to these publications. Comprised are likewise the corresponding stereoisomers as well as the corresponding crystal modifications, e.g. solvates and polymorphs, which are disclosed therein. The term nateglinide as used herein comprises crystal modifications (polymorphs) such as those disclosed in EP 0526171 B1 or US 5,488,510, respectively, the subject matter of which is incorporated by reference to this application, especially the subject matter of claims 8 to 10 as well as the corresponding references to the B-type crystal modification. Preferably, in the present invention the B- or H-type, more preferably the H-type, is used.

It will be understood that in the discussion of methods, references to the active ingredients are meant to also include the pharmaceutically acceptable salts. If these active ingredients have, for example, at least one basic center, they can form acid addition salts. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. The active ingredients having an acid group (for example COOH) can also form salts with bases. For example the active ingredients to be combined can be present as a sodium salt or as a maleate. The active ingredient or a pharmaceutically acceptable salt thereof may also be used in form of a hydrate or include other solvents used for crystallization.

MCC555 can be formulated as disclosed on page 49, lines 30 to 45, of EP 0 604 983 B1; englitazone as disclosed from page 6, line 52, to page 7, line 6, or analogous to Examples

27 or 28 on page 24 of EP 0 207 605 B1; and darglitazone and BM-13.1246 can be formulated as disclosed on page 8, line 42 to line 54 of EP 0 332 332 B1. AY-31637 can be administered as disclosed in column 4, lines 32 to 51 of US 4,997,948 and rosi glitazone as disclosed on page 9, lines 32 to 40 of EP 0 306 228 A1, the latter preferably as its maleate salt. Corresponding to the needs of the single patient and under the proviso that it is intended by a physician to administer the combinations, e.g. the pharmaceutical compositions, in separate tablets, it is possible to administer the antidiabetics as launched, e.g. rosiglitazone in the form as it is launched under the trademark AVANDIA ™. Troglitazone can be administered in the form as it is launched under the trademarks ReZulin™, PRELAY™, ROMOZIN™ (in the United Kingdom) or NOSCAL™ (in Japan). Pioglitazone can be administered as disclosed in Example 2 of EP 0 193 256 A1, preferably in the form of the monohydrochloride salt or in the form as launched under the trademark ACTOS™. Ciglitazone can, for example, be formulated as disclosed in Example 13 of US 4,287,200. Acarbose can be administered in the form as it is marketed e.g. under the trademark GLUCOBAY™. If the drug metformin shall be administered in a separate pharmaceutical composition, it can be administered in the form as it is launched e.g. under the trademark DIABETOSAN™. If the drug metformin shall be administered in a separate pharmaceutical composition in the form of its hydrochloride salt, the metformin hydrochloride salt can be administered in the form as it is launched e.g. under the trademarks DIABETASE 500™, DIABETASE 850™ or GLUCOPHAGE S™. The preparation of metformin (dimethyldiguanide) and its hydrochloride salt is state of the art and was disclosed first by Emil A. Werner and James Bell, J. Chem. Soc. 121, 1922, 1790-1794. Glyburide can be taken in the form as it is launched under the trademark AZUGLUCON ™ or EUGLUCON™. Tolbutamide can be administered in the form as it is launched under the trademark ORABET, glimepiride as launched under the trademark AMARYL ™, gliclazide as launched under the trademark DIAMICRON™, glibornuride as launched under the trademark GLUBORID™ and gliquidone as it is launched under the trademark GLURENORM™.

The nature of diabetes and related diseases or conditions is multifactorial. Under certain circumstances, drugs with different mechanisms of action may be combined. However, just considering any combination of drugs having different mode of action but acting in th similar field does not necessarily lead to combinations with advantageous effects.

All the more surprising is the experimental finding that the combined administration of nateglinide or a pharmaceutically acceptable salt thereof and (a) an antidiabetic phenylacetic acid derivative or (b) acarbose, results not only in a beneficial, especially a synergistic, therapeutic effect but also in additional benefits resulting from combined treatment such as a surprising prolongation of efficacy, a broader variety of therapeutic treatment and surprising beneficial effects on diseases and conditions associated with diabetes, e.g. less gain of weight, compared to a monotherapy applying only one of the pharmaceutically active compounds used in the combinations disclosed herein.

It can be shown by established test models and especially those test models described herein that the combination of nateglinide and (a) an antidiabetic phenylacetic acid derivative or (b) acarbose, or in each case a pharmaceutically acceptable salt thereof, results in a more effective prevention or preferably treatment of diseases, especially metabolic disorders, and in particular type 2 diabetes mellitus and di seases and conditions associated with diabetes mellitus.

If taken simultaneously, this results not only in a further enhanced beneficial, especially a synergistic, therapeutic effect, but also in additional benefits resulting from the simultaneous treatment such as a surprising prolongation of efficacy, a broader variety of therapeutic treatment and surprising beneficial effects, e.g. less increase of weight, on diseases and conditions associated with diabetes mellitus, for the combinations as described herein. Moreover, for a human patient, especially for elderly people, it is more convenient and easier to remember to take two tablets at the same time, e.g. before a meal, than staggered in time, i.e. according to a more complicated treatment schedule. More preferably, both active ingredients are administered as a fixed combination, as applied in a unit dosage form, e.g., in such a case as a single tablet, in all cases described herein. Taking a single tablet is even easier to handle than taking two tablets at the same time. Furthermore, the packaging can be accomplished with less effort. Accordingly, the present invention relates in particular to a fixed combination comprising (i) nateglinide and acarbose or (ii) nateglinide and repaglinide.

The person skilled in the pertinent art is fully enabled to select a relevant animal test model to prove the hereinbefore and hereinafter indicated therapeutic indications and beneficial

effects. The pharmacological activity may, for example, be demonstrated following essentially an *in-vivo* test procedure in mice or in a clinical study as described hereinafter.

In-vivo test in mice for blood glucose control

ICR-CDI mice (male, five weeks old, body weight: about 20 g) are abstained from food for 18 hours, and then used as test subjects. A combination according to the present invention and the active ingredients alone are suspended in 0.5% CMC-0.14M sodium chloride buffer solution (pH 7.4). The solution thus obtained is administered orally in fixed volume amounts to the test subjects. After predetermined time, the percentage decrease of the blood glucose against the control group is determined.

Clinical double-blind, randomized, parallel-group study in subjects with non-insulin dependent diabetes mellitus (type 2 diabetes mellitus) inadequately controlled on diet alone

These studies prove, e.g., the synergism of the claimed composition, especially combined preparation or pharmaceutical composition, respectively. The beneficial effects on diseases and conditions associated with diabetes as defined in this application can be determined directly through the results of these studies or by changes in the study designs which are known as such to a person skilled in the art.

The studies are, in particular, suitable to assess the effects of monotherapy with nateglinide or with (a) an antidiabetic phenylacetic acid or with (b) acarbose or a combination of these substances on glycemic control. Subjects with a diagnosis of type 2 diabetes mellitus who have not achieved near normoglycemia (HbA_{1c} (glycosylated haemoglobin) <6.8%) on diet only are chosen for these trial. The effects on glycemic control achieved with nateglinide monotherapy, monotherapy with an antidiabetic phenylacetic acid, monotherapy with acarbose and the combination therapy of nateglinide plus (a) an antidiabetic phenylacetic acid derivative or (b) acarbose are determined in these studies with the control achieved on placebo, all subjects continuing with the same diet as in the period before treatment. Measures of glycemic control are validated surrogate endpoints for the treatment of diabetes. HbA_{1c} is the singl most reliable measurement for assessing glycemic control (D. Goldstein et al, Tests of Glycemia in Diabetes; Diabetes Care 1995, 18(6), 896-909) and is the primary response variable in this study. Since glycosylation of hemoglobin is determined

by the glucose concentration at the time each red blood cell is made, HbA_{1c} provides an estimate of mean blood glucose for the previous three months.

In the repaglinide study before starting with the double-blind treatment for 24 weeks, the subjects are administered for four weeks nateglinide matching placebos before breakfast, lunch and dinner, and a placebo matching repaglinide administered later on with breakfast, lunch and dinner (period I). The subjects are then separated into four treatment groups for the 24-week double-blind study (period II) as depicted in Table 1. Approximately 170 subjects are randomized per treatment group. The total study duration including the run-in period for each subject is 28 weeks. Statistical analysis can be carried out by methods known in the art.

Table 1: Examples for a Combination comprising Repaglinide

nateglinide (I) 120 mg* + repaglinide placebo*
repaglinide 1 mg* + nateglinide (I) placebo*
nateglinide (I) 120 mg* + repaglinide 1 mg*
nateglinide (I) placebo* + repaglinide placebo*

* administered before breakfast, lunch, and dinner

Nateglinide tablets contain either 120 mg or matching placebo. Repaglinide 1 mg tablets can be purchased commercially and overencapsulated to match the corresponding placebo capsules.

Nateglinide / Acarbose combination studies

The acarbose combination studies are double-blind, randomized, parallel-group, studies comparing efficacy, tolerability and safety of nateglinide and acarbose alone with the combination of acarbose and nateglinide in 140 subjects with Type 2 diabetes inadequately controlled on diet alone. The duration of this study for each patient is 28 weeks. Following a run-in period of 4 weeks, patients are randomized (1:1 ratio) to one of the two double-blind

treatment arms for 24 weeks. No placebo is given during the run-in period.

Table 2: Examples for a Combination comprising 100 mg Acarbose

nateglinide 120 mg* + acarbose placebo**
acarbose 100 mg** + nateglinide placebo*
nateglinide 120 mg* + acarbose 100 mg**
nateglinide placebo* + acarbose placebo**

* administered before breakfast, lunch, and dinner

** administered together with the first bite of breakfast, lunch and dinner

Because nateglinide is dispensed as tablets (120 mg or placebo) and acarbose as capsules (50 mg or placebo) blinding will be achieved by using a double-dummy design and patients will take either 1 tablet nateglinide 120 mg and 1 or 2 capsules acarbose placebo or 1 tablet nateglinide placebo and 1 or 2 capsules acarbose 50 mg.

Table 3: Examples for a Combination comprising 50 mg Acarbose

nateglinide 120 mg* + acarbose placebo**
acarbose 50 mg** + nateglinide placebo*
nateglinide 120 mg* + acarbose 50 mg**
nateglinide placebo* + acarbose placebo**

* administered before breakfast, lunch, and dinner

** administered together with the first bite of breakfast, lunch and dinner

Nateglinide tablets contain either 120 mg or matching placebo. acarbose as capsules (50 mg) can be purchased commercially and overencapsulated to match the corresponding placebo capsules.

For example, the following procedure can be followed in order to tak blood samples: The subject is advised not to take the morning dose of study medication or eat breakfast on the

day of a scheduled study visit. The morning dose is administered by site personnel after the collection of all fasting laboratory samples and completion of all study procedures. Visits are scheduled to be performed at 2 week intervals during period I, and 4 to 8 week intervals during period II. Subjects have fasted for at least 7 hours at the time of each visit. All blood samples for laboratory evaluations are drawn between 7:00 AM and 10:00 AM. All tests are conducted in accordance with GLP (Good Laboratory Practice) principles following procedures known in the art.

HbA_{1c} is measured by High Performance Liquid Chromatography (HPLC) using the ion-exchange method on a Bio-Rad Diamat analyzer. A back-up affinity method are used if hemoglobin variants or hemoglobin degradation peaks are observed.
Further parameters to be determined are fasting plasma glucose (FPG), fasting lipids (total, HDL (high density lipoprotein)- and LDL (low density lipoprotein)-cholesterol, and triglycerides) and body weight. FPG will be measured using the hexokinase method and LDL-cholesterol will be calculated using the Friedewald formula if triglycerides are < 400 mg/dL (4.5 mmol/l).
Various parameters of the study described above can be modified, e.g. in order to optimize the dosage for special diseases or indications mentioned herein, to cope with tolerability problems during the study or to obtain similar or identical results with less efforts. For example, a different subject population can be involved in such a clinical trial, e.g. subjects with a diagnosis of type 2 diabetes mellitus who have achieved near normoglycemia (HbA_{1c} <6.8%) on diet alone, subjects with diseases other than diabetes mellitus, e.g. other metabolic disorders, or subjects selected by other criteria, such as age or sex; the subject number can be decreased, e.g. to a number of between 70 and 150, especially 100 or 120, subjects per treatment group; treatment groups can be deleted, i.e. for example to carry out a study with a comparison of the combination of nateglinide and an antidiabetic phenylacetic acid versus the single antidiabetic phenylacetic acid only; the term of the placebo run-in period (period I) can be changed, i.e. it can be extended, shortened or deleted; the visit schedule can be extended, e.g. to every 10, 12 or 14 weeks; the visit instructions can be changed, e.g. the instruction that blood samples for laboratory evaluations have to be drawn between 7:00 AM and 10:00 AM; HbA_{1c} can be determined by other means; or one or more of the parameters to b determined during the study mentioned above, e.g. (FPG) or fasting lipids, can be deleted or the determination of additional parameters (see below) can be added.

Additional parameters can be determined in the course of the study, e.g. by additional tests. Such additional tests can comprise the analysis of body liquids in order to determine amounts or numbers for parameters such as those listed below and can serve e.g. the purpose of determining the tolerability of the administered active ingredients: determination of hematocrit and hemoglobin, platelet count, erythrocyte count, total and differential leukocyte count (basophils, eosinophils, lymphocytes, monocytes, segmented neutrophils and total neutrophils); determination of albumin, alkaline phosphatase, alanine amino transferase (serum glutamic pyruvic transaminase), aspartate amino transferase (serum glutamic oxaloacetic transaminase), blood urea nitrogen or urea, bicarbonate, calcium, chloride, total creatine phosphokinase (CPK), creatine phosphokinase muscle-brain fraction isoenzyme (if CPK is elevated), direct bilirubin, creatinine, γ-glutamyl transferase, lactate dehydrogenase, potassium, sodium, total bilirubin, total protein and uric acid in the blood; determination of bilirubin, glucose, ketones, pH, protein, and specific gravity in the subjects urine; determination of body weight, blood pressure (systolic and diastolic, after 3 minutes sitting) and radial pulse (after 3 minutes sitting).

The results clearly show that the combinations according to the present invention can be used for the prevention, delay of progression and preferably the treatment of metabolic disorders and in particular diabetes, especially type 2 diabetes mellitus and diseases and conditions associated with diabetes. The combinations of the present invention can also be used for the prevention and preferably the treatment of other diseases.

The combined administration of nateglinide and (a) an antidiabetic phenylacetic acid derivative or (b) acarbose results in a beneficial, especially a synergistic, therapeutic effect, especially on type 2 diabetes, and also in additional benefits such as a decrease of diabetes-related mortality, a surprising prolongation of efficacy of the drug (such delaying the eventual need for insulin), a broader variety of therapeutic treatment, maintaining the target blood glucose level in type 2 diabetes patients, providing a good initial blood glucose control in type 2 diabetes patients, only modest changes in fasting plasma glucose level, and further surprising beneficial effects, comprising e.g. less or no gain of body weight, a decrease of gastrointestinal side effects or an improved safety profile, compared to a monotherapy applying only one of the pharmaceutically active compounds used in the combinations disclosed herein. In particular, the further surprising beneficial effects can also

be observed during the treatment of metabolic disorders other than type 2 diabetes and during the treatment of diseases and conditions associated with type 2 diabetes. Further benefits are, e.g., that lower doses of the individual drugs to be combined accor ding to the present invention can be used to reduce the dosage, for example, that the dosages need not only often be smaller but are also applied less frequently, or can be used in order to diminish the incidence of side effects (e.g. anaemia, oedema, headache).

Furthermore, in a number of combinations as disclosed herein the side-effects observed with one of the components surprisingly do not accumulate on application of the combination.

The beneficial therapeutic effects, additional benefits and also the surprising beneficial effects are observed especially in human subjects suffering from a more severe form of type 2 diabetes, i.e. human subjects having an elevated HbA_{1c} value at baseline of greater 8 % and more particular in human subjects having a HbA_{1c} value at baseline of greater than 9.5 %, before treatment with the combinations described herein. Nateglinide is administered to such human patients preferably in a dose of between 90 and 200 mg, more preferably between 100 and 150 mg, for example 120 mg, nateglinide per meal as part of the combination given to them.

In one preferred embodiment of the invention, a dose of between 45 and 85 mg, more preferably 60 mg, of nateglinide per meal is administered as part of the combination with repaglinide or acarbose to human subjects having a HbA_{1c} value at baseline between 6.8 % and 8 %, in particular between 6.8 % and 7%. This provides the option to increase the amount of nateglinide later on, which option is advantegous especially in a situation when the HbA_{1c} value at baseline exceeds values of 7% after starting the treatment of the human subject for a period of time or constantly or if the responsible physician determines that the treatment schedule has to be changed to higher amounts of nateglinide for other reasons.

Furthermore, the beneficial therapeutic effects, additional benefits and also the surprising beneficial effects ar observed especially in human subjects having a body mass index (BMI) of 20 to 35 kg/m^2, in particular a BMI of 27 to 35 kg/m^2, and even more enhanced in human subjects with a BMI of 30 to 35 kg/m^2. Human subjects having a BMI greater 30 kg/m^2 ar defined to be clinically obese.

Additionally, the beneficial therapeutic effects, additional benefits and also the surprising beneficial effects are observed especially in patients poorly controlled by monotherapy with one of the components of the combinations disclosed herein.

Furthermore, the present invention relates to a combined preparation which comprises nateglinide and (a) an antidiabetic phenylacetic acid derivative or (b) acarbose in which the active ingredients are present in each case in free form or in the form of a pharmaceutically acceptable salt and optionally at least one pharmaceutically acceptable carrier, as a combined preparation for simultaneous, separate or sequential use in the prevention or treatment of diseases, especially metabolic disorders, more especially diabetes and in particular type 2 diabetes mellitus, and diseases and conditions associated with diabetes.

Preferred antidiabetic phenylacetic acid derivatives are those represented by formula (II), wherein
R_1 is C_4-C_6-alkylenimino which is unsubstituted or substituted by one or two lower alkyl groups,
R_2 is hydrogen, halogen, methyl or methoxy,
R_3 is hydrogen, lower alkyl; or phenyl which is unsubstituted or substituted by halogen, methyl or methoxy,
R_4 is hydrogen, allyl, acetyl, propionyl; or lower alkyl which is unsubstituted or substituted by phenyl, and
W is methyl, hydroxymethyl, formyl, carboxy or lower alkoxycarbonyl, in which the alkoxy moiety can be substituted by phenyl.

Unless stated otherwise, in the present disclosure organic radicals and compounds designated "lower" contain not more than 7, preferably not more than 4, carbon atoms.

Halogen represents preferably fluoro, chloro or bromo.

Lower alkyl is, if not stated otherwise, preferably ethyl or, most preferably, methyl.

Lower alkoxy is preferably methoxy or thoxy.

C_4-C_6-Alkylenimino which is unsubstituted or substituted by one or two lower alkyl groups is, for example, pyrrolidinyl, methylpyrrolidinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 2-methyl-1-piperidinyl or hexamethylenimino. Preferably, C_4-C_6-alkylenimino is 1-piperidinyl.

In a preferred embodiment of the invention the antidiabetic derivatives are represented by formula (II), wherein
R_1 is piperidinyl,
R_2 is hydrogen, fluoro or chloro,
R_3 is methyl, ethyl, n-propyl, iso-propyl, 2-methylpropyl, n-butyl, tert-butyl, n-pentyl, n-hexyl or phenyl,
R_4 is methyl or ethyl, and
W is carboxy, methoxycarbonyl or ethoxycarbonyl.

In a very preferred embodiment of the invention the antidiabetic phenylacetic acid derivative is repaglinide or a pharmaceutically acceptable salt thereof.

Preferably, the antidiabetic thiazolidinedione derivative is selected from the group consisting of MCC555, T-174, KRP297, and, more preferably, rosiglitazone, pioglitazone and troglitazone, or a pharmaceutically acceptable salt thereof.

It is one objective of this invention to provide a pharmaceutical composition comprising a amount, which is jointly therapeutically effective against metabolic disorders, more especially diabetes and in particular type 2 diabetes mellitus or a disease or condition associated with diabetes, of (i) nateglinide or a pharmaceutically acceptable salt thereof and (ii) (a) an antidiabetic phenylacetic acid derivative or (b) acarbose or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable carrier. In this composition, components (i) and (ii) can be administered together, one after the other or separately in one combined unit dosage form or in two separate unit dosage forms. The unit dosage form may also be a fixed combination.

The pharmaceutical compositions according to the invention can be prepared in a manner known per se and are those suitable for enteral, such as oral or rectal, and parenteral administration to mammals (warm-blooded animals), including man, comprising a

therapeutically effective amount of the pharmacologically active compound, alone or in combination with one or more pharmaceutically acceptable carries, especially suitable for enteral or parenteral application.

The novel pharmaceutical preparations contain, for example, from about 10 % to about 100 %, preferably 80%, preferably from about 20 % to about 60 %, of the active ingredient. Pharmaceutical preparations for the combination therapy that may be used for enteral or parenteral administration are, for example, those in unit dose forms, such as sugar-coated tablets, tablets, capsules or suppositories, and furthermore ampoules. If not indicated otherwise, these are prepared in a manner known per se, for example by means of conventional mixing, granulating, sugar-coating, dissolving or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active ingredient with solid carriers, if desired granulating a mixture o btained, and processing the mixture or granules, if desired or necessary, after addition of suitable excipients to give tablets or sugar-coated tablet cores.

It will be appreciated that the unit content of active ingredient or ingredients contained in an individual dose of each dosage form need not in itself constitute an effective amount since the necessary effective amount can be reached by administration of a plurality of dosage units.

In particular, a therapeutically effective amount of each of the components of the combination of the present invention may be administered simultaneously or sequentially and in any order, and the components may be administered separately or as a fixed combination. For example, the method of prevention, delay of progression or treatment of according to the invention may comprise (i) administration of nateglinide in free or pharmaceutically acceptable salt form and (ii) adminstration of (a) an antidiabetic phenylacetic acid derivative or (b) acarbose in free or pharmaceutically acceptable salt form, simultaneously or sequentially in any order, in jointly therapeutically effective amounts, preferably in synergistically effective amounts, e.g. in daily dosages corresponding to the ratios described herein. The individual components of the combination can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. For example, in a two-component combination of, e.g., nateglinide and acarbose, treatment with nateglinide can commence

prior to, subsequent to or concurrent with commencement of treatment with acarbose. Furthermore, the term administering also encompasses the use of prodrugs of any of the anti-diabetic drugs that convert in vivo to the selective anti-diabetic drug. The instant invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly.

The preferred route of administration of the dosage forms of the present invention is orally or enterally. In practical use, the anti-diabetic drugs or combinations thereof can be combined as the active ingredients in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents; or carriers such as starches, sugars, microcristalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, capsules and tablets, with the solid oral preparations being preferred over the liquid preparations. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

The effective dosage of each of the active ingredients employed in the combination therapy may vary depending on the particular compound or pharmaceutical composition employed, the mode of administration, the condition being treated , the severity of the condition being treated. Thus, the dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including the route of administration and the renal and hepatic function of the patient. A physician, clinician or veterinarian of ordinary skill can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition. Optimal precision in achieving concentration of drug within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the drug's availability to target sites. This involves a consideration of the distribution, equilibrium, and elimination of a drug.

If the active ingredients are administered, the composition, in particular pharmaceutical composition, comprising solely nateglinide can be produced by a process that comprises granulating in the presence of water to form granules, drying the granules, and optionally screening the granules, for example, through a wire mesh screen. All of the ingredients of the composition may be added prior to or during the granulation. Alternatively, all or a portion of one or more of the ingredients may be added after the granulation step is complete. For example, all or a portion of anti-adherent (e.g., silica), all or a portion of lubricant (e.g., magnesium stearate) and/or all or a portion of disintegrant (e.g., crosca - rmellose or any salt thereof) may be added after the granulation. In one aspect of the invention, all ingredients except the magnesium stearate and the colloidal silica are loaded into the granulator, then they are added later. The process of producing th is composition, in particular pharmaceutical composition, may be performed without the need for a pulver - ization step. As used herein, the terms "pulverization" and "pulverize" refer to any process that involves the grinding or smashing cutting of particles to reduce the particles' size. The composition, in particular pharmaceutical composition, is capable of being produced without pulverizing the granules between the granulation step and the drying and/or compression step used to form the granules into a tablet.

A further aspect of the present invention is the use of a pharmaceutical composition comprising nateglinde and (a) an antidiabetic phenylacetic acid derivative or (b) acarbose in each case in free form or in form of a pharmaceutically acceptable salt thereof for the preparation of a medicament for the prevention, delay of progression or treatment of metabolic disorders, in particular of type 2 diabetes mellitus or a disease or condition associated with diabetes mellitus.

Further aspects of the present invention are oral dosage forms and pharmaceutical formulations (compositions) for administration to mammals suffering from or at risk for diseases having the characteristics of type 2 diabetes. It will be understood that any statistically significant attenuation in the disease symptoms of type 2 diabetes pursuant to the treatment of the present invention is within the scope of the invention.

The term "combination therapy" as used herein means that a combination which comprises nateglinide and (a) an antidiabetic phenylacetic acid derivative or (b) acarbose, is used for

the treatment, delay of progression or prevention of one of the diseases, especially metabolic disorders, mentioned herein.

In accordance with the combination therapies of the present invention there is further provided a method of prevention, delay of progression or treatment of and a pharmaceutical composition for the prevention, delay of progression or treatment of obesity and diabetes. The treatment involves administering to a patient in need of such treatment a pharmaceutical composition comprising a pharmaceutical carrier and a therapeutically effective amount of each compound in the combination of the present invention.

Furthermore, the invention relates to a pharmaceutical composition comprising nateglinde and (a) an antidiabetic phenylacetic acid derivative or (b) acarbose in each case in free form or in form of a pharmaceutically acceptable salt thereof for the prevention, delay of progression or treatment of hyperglycemia, hyperinsulinaemia, hyperlipidaemia, insulin resistance, impaired glucose metabolism, obesity, diabetic retinopathy, macular degeneration, cataracts, diabetic nephropathy, glomerulosclerosis, diabetic neuropathy, erectile dysfunction, premenstrual syndrome, vascular restenosis, ulcerative colitis, coronary heart disease, hypertension, angina pectoris, myocardial infarction, stroke, skin and connective tissue disorders, foot ulcerations, metabolic acidosis, arthritis, osteoporosis and in particular conditions of impaired glucose tolerance and especially type 2 diabetes.

A further aspect of the present invention is a method of treatment of a warm-blooded animal, especially a human, having metabolic disorders, in particular type 2 diabetes mellitus or a disease or condition associated with diabetes mellitus, comprising administering to the animal a combination of nateglinide and (a) an antidiabetic phenylacetic acid derivative or (b) acarbose in an amount which is jointly therapeutically effective against metabolic disorders in which both compounds can also be pr esent in the form of their pharmaceutically acceptable salts simultaneously or sequentially in any order, separately or in a fixed combination. In this context, the term "method of treatment" includes a method of prevention of a disease, i.e. the prophylactic administration of the combination, such as a combined preparation or pharmaceutical composition, to healthy patients to prevent the outbreak of the diseases and conditions mentioned herein. The combination is preferably administered simultaneously. In particular, the invention relates to such a method wherein nateglinide and acarbose or nateglinide and the antidiabetic phenylacetic acid are

provided as a combined preparation in which case the disease or condition associated with diabetes is preferably selected from the group con sisting of hyperglycemia, hyperinsulinaemia, hyperlipidaemia, insulin resistance, impaired glucose metabolism, obesity, diabetic retinopathy, macular degene ration, cataracts, diabetic nephropathy, glomerulosclerosis, diabetic neuropathy, erectile dysfunction, premenstrual syndrome, coronary heart disease, hypertension, angina pectoris, myocardial infarction, stroke, vascular restenosis, skin and connective tissue disorders, foot ulcerations and ulcerative colitis.

The invention relates also to a combination as disclosed herein for use in the prevention, delay of progression or treatment of diseases, the use of such combination for the preparation of a medicament for the prevention, delay of progression or treatment of metabolic disorders, and the use of such combination for the cosmetic treatment of a mammal in order to effect a cosmetically beneficial loss of body weight.

Furthermore, the invention relates to a method of improving the bodily appearance of a mammal, including man, especially man suffering from a metabolic disorder, in particular type 2 diabetes, which comprises orally administering to said mammal a combination, e.g. as a combined preparation or as a composition, as described herein or in a dosage effective to influence, e.g. to increase or decrease, the glucose metabolism, or to influence the body weight by other mechanisms, and repeating said dosage until a cosmetically beneficial loss of body weight has occurred. Such combinations described herein can also be used to prevent, for cosmetic reasons, a further increase in body weight in humans experiencing such an increase. Moreover, the invention relates to the combinations described herein useful for improving the bodily appearance of a mammal, especially a human being, and the use of such combinations in order to improve the bodily appearance of a mammal, especially a human being. Overweight is one of the risk factors for developing a metabolic disorder, in particular type 2 diabetes, and at the same time often the result of such a metabolic disorder, especially type 2 diabetes. Furthermore, a number of antidiabetics are known to cause weight gain. Hence, humans suffering from metabolic disorders, especially type 2 diabetes, are often faced with overweight. Therefore, the cosmetically beneficial loss of body weight can be effected especially in humans suffering from a m tabolic disorder, such as type 2 diabet s. The combinations, e.g. a combined preparation or a composition, described h rein can also be used to replace or complement

an antidiabetic drug taken by a human suffering from type 2 diabetes in order to prevent, for cosmetic reasons, a further increase of the body weight.

The invention relates in particular to a commercial package comprising jointly therapeutically effective amounts of nateglinide, in free or pharmaceutically acceptable salt form, and (a) an antidiabetic phenylacetic acid derivative or (b) acarbose, in free or pharmaceutically acceptable salt form in each case, together with instructions for use thereof in the treatment of metabolic disorders, more especially diabetes and in particular type 2 diabetes mellitus or a disease or condition associated with diabetes .

The dosage regimen of any of the individual components of the combination s disclosed herein may be adjusted to provide the optimal therapeutic response. The exact amount of the pharmaceutically active compounds mentioned below, the specific dose level and frequency of dosage for any particular patient may vary depending upon factors known to the person skilled in the art including species of the warm-blooded animal, body weight , sex, diet and age, the nature and severity of the condition to be treated, the mode of administration and the particular combination to be employed. In particular, the dosage range of the combination of nateglinide and (a) an antidiabetic phenylacetic acid derivative or (b) acarbose to be employed depends upon factors known to the person skilled in the art including species of the warm-blooded animal, body weight and age, the nature and severity of the condition to be treated, the mode of administration and the particular substance to be employed. Unless stated otherwise herein, nateglinide and (a) an antidiabetic phenylacetic acid derivative or (b) acarbose are preferably divided and administered from one to four times per day, preferably the combination is taken together with or, preferably, before every meal. Unless stated otherwise herein, nateglinide and (a) an antidiabetic phenylacetic acid derivative or (b) acarbose are preferably divided and administered from one to four times per day.

Nateglinide is preferably administered to the warm-blooded animal in a dosage in the range of about 5 to 1200, more preferably 10 to 1000 and most preferably 25 to 800 mg/day, especially when th warm-blooded animal is a human of about 70 kg body weight.

If the the warm-blooded animal is a human the dosage of the antidiabetic phenylacetic acid derivative is preferably in the range of about 0.25 to 100, more preferably about 0.5 to 40,

and most preferably 1 to 20, mg/day, per adult patient. In the case of repaglinide, for example, the dosage is preferably in the range of about 0.5 to 16, and most preferably 1 to 8, mg/day, per adult patient.

If the the warm-blooded animal is a human the dosage of acarbose is preferably in the range of about 50 to 600, more preferably about 150 to 300, mg/day, per adult patient.

The ratio of the daily doses of nateglinde or a pharmaceutically acceptable salt thereof to (a) an antidiabetic phenylacetic acid derivative or (b) acarbose may vary within wide limits depending, e.g., on the nature of the antidiabetic phenylacetic acid selected. In order to obtain a synergistic effect of the components, preferably the ratio of nateglinide or a pharmaceutically acceptable salt thereof to the antidiabetic phenylacetic acid derivative is between 4800:1 and 1:20. For example the ratio of nateglinide or a pharmaceutically acceptable salt thereof to repaglinide is preferably between 1600:1 and 1.5:1, and more preferably between 800:1 and 3:1. The ratio of the daily doses of nateglinide or a pharmaceutically acceptable salt thereof to acarbose may vary within wide limits depending in particular on the needs of the warm-blooded animal treated. In order to obtain a synergistic effect of the components, preferably the ratio of nateglinide or a pharmaceutically acceptable salt thereof to acarbose is between 24:1 and 1:120, more preferably between 5:1 and 1:12.

The following Examples illustrates the invention described above; they are not, however, intended to limit the scope of the invention in any way.

Example 1: Tablets of Nateglinide

108,000 tablets, each which contain 120 mg of nateglinide are prepa red as follows:

Composition:	nateglinide	12.960 kg
	lactose, NF	30.564 kg
	microcrystalline cellulose, NF	15.336 kg
	povidone, USP	2.592 kg
	croscarmellose sodium, NF	3.974 kg

colloidal silicon dioxide, NF	1.382 kg
magnesium stearate, NF	1.231 kg
coating: opadry yellow	1.944 kg
purified water, USP*	Q.S.

*: removed during process

Preparation process: The microcrystalline cellulose, povidone, part of the croscarmellose sodium, nateglinide and lactose are mixed in a high shear mixer and afterwards granulated using purified water. Alternatively, the microcrystalline cellulose, povidone, a portion of the croscarmellose sodium, nateglinide and lactose are granulated in a collette gral granulator with the addition of purified water. The wet granules are dried in a fluid bed dryer and passed through a screen. The colloidal silicon dioxide and the rest of the croscarmellose sodium are mixed, passed through a screen and blended with the dried granules in a V-blender. The magnesium stearate is passed through a screen, blended with the blend from the V-blender and afterwards the total mixture is compressed to tablets. The opadry yellow is suspended in purified water and the tablets are coated with the coating suspension.

Example 2: Galenic Formulation of Nateglinide No. 1

intra-granular:	
nateglinide	120 mg
lactose monohydrate	283 mg
microcrystalline cellulose	142 mg
povidone	24 mg
croscarmellose sodium	24 mg
extra-granular:	
magnesium stearate	7 mg
opadry white	20 mg

Example 3: Galenic Formulation of Nateglinide No. 2

intra-granular:	
nateglinide	120 mg

lactose monohydrate	283 mg
microcrystalline cellulose	142 mg
povidone	24 mg
croscarmellose sodium	24 mg
extra-granular:	
croscarmellose sodium	12.8 mg
magnesium stearate	11.4 mg
opadry yellow	18.0 mg
colloidal silicon dioxide	12.8 mg

Example 4: Tablets of Nateglinide

108,000 tablets, each which contain 120 mg of nateglinide are prepared as follows:

Composition:	nateglinide	12.960 kg
	lactose, NF	30.564 kg
	microcrystalline cellulose, NF	15.336 kg
	povidone, USP	2.592 kg
	croscarmellose sodium, NF	3.974 kg
	colloidal silicon dioxide, NF	1.382 kg
	magnesium stearate, NF	1.231 kg
	coating: opadry yellow	1.944 kg
	purified water, USP*	Q.S.

*: removed during process

Preparation process: The microcrystalline cellulose, povidone, a portion of the croscarmellose sodium, nateglinide and lactose are granulated in a collette gral granulator with the addition of purified water. The wet granules are dried in a fluid bed dryer and passed through a screen. The colloidal silicon dioxide and the rest of the croscarmellose sodium are mixed, passed through a screen and blended with the dried granules in a V-blender. The magnesium stearate is passed through a screen, bl nded with the blend from the V-blender and afterwards the total mixture is compressed to tablets. The opadry yellow is suspended in purified water and the tablets are coated with the coating suspension. Variants of this process include adding the colloidal silica and the remaining croscarmellose

sodium to the second granulator load after drying, then screening together; and combining as many as 3 granulator/drier loads per batch.

Example 5: Pharmaceutical composition of Nateglinide (120 mg)

nateglinide	120 mg
lactose monohydrate	283 mg
microcrystalline cellulose	142 mg
Povidone	24 mg
croscarmellose sodium	36.8 mg
magnesium stearate	11.4 mg
opadry yellow	18.0 mg
colloidal silicon dioxide	12.8 mg